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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,186	KERKMANN-TUCEK, AIDA	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on th cov r sheet with th corr spondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-5,9 and 10* is/are rejected.

7)☐ Claim(s) *6-8 and 11-13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Pri rity under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13 are pending and examined on the merits.

Claims 6-8 and 11-13 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot serve as the basis for another multiple-dependent claim . See MPEP § 608.01(n). Accordingly, the claims 6-8 and 11-13 have not been further treated on the merits.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter as the claims can read on cells that exist within mammals.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 9 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) The metes and bounds of claims 1 and 8 cannot be determined. Claims 1 and 9 recite "a combination of MHC I and MHC II genes, occurring in humans". It is unclear if the limitation of "occurring in humans is to be applied to the origin of the MHC genes, or the origin of the tumor cells, or if "occurring in humans" refers to an analogous occurrence in humans, such as the mouse genes encoding MHC I and II correspond to the HLA genes of humans. for purpose of examination, all alternative will be considered.

(B) Claim 2 is vague and indefinite in the recitation of "expressed for co-stimulatory molecules". It is unclear if this means that the genes directly express co-stimulatory molecules, or that the expression of the genes indirectly affects the expression of costimulatory molecules.

(C) It is unclear how claim 3 limits claim 2. Claim 2 recites "wherein one or several genes are also expressed for co-stimulatory molecules". claim 3 recites "wherein the costimulatory molecules comprise B7 and CD44". It is unclear if the metes and bounds of claim 3 entails the expression of both B7 and CD44, or if applicant intends that either B7 or CD44 are expressed. For purpose of examination, both alternatives will be considered.

(D) Claim 4 is vague and indefinite in the recitation of "expressed for cytokines". It is unclear if this means that the genes directly express the cytokines, or that the expression of the genes indirectly affects the expression of cytokines.

(E) It is unclear how claim 5 limits claim 4. Claim 4 recites "wherein one or several genes are also expressed for cytokines". claim 5 recites "wherein the cytokines are interleukins, GM-CSF, TNF-alpha and interferon-gamma". It is unclear if the metes and bounds of claim 5 entails the expression of all of interleukins, GM-CSF, TNF-alpha and interferon-gamma, or if applicant intends that either interleukins, GM-CSF, TNF-alpha or interferon-gamma are expressed. For purpose of examination, both alternatives will be considered.

(F) It is unclear how the first active method step of claim 9, "tissue typing of tumor cells" relates to the method objective or producing tumor cells according to claim 1, or to the subsequent active method steps in claim 9. It is further unclear how the active method step (c), which requires the selection for tumor cells which express both the MHC I and MHC II genes, can be applied to the product resulting from the active method step of (b) which allows for the transfection of either MHC I or MHC II genes. Further, the metes and bounds of what constitutes "tissue typing" is not defined and can read on the simple determination of the presence or absence of MHC I and MHC II or it can read on the identification of the specific histocompatibility genes present in the same (i.e. HLA-2.1).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Ostrand-Rosenburg et al (Journal of Immunogenics, 1989, Vol. 16, pp. 343-349).

Claim 1 is drawn to tumor cells comprising a combination of MHC I and MHC II genes, occurring in humans, which genes are expressed. Claim 9 is drawn to a method of producing the tumor cells according to claim 1 comprising tissue typing of tumor cells, transfection of the tumor cells with MHC I and/or MHC II genes so as to obtain a combination of these genes occurring in humans, and selection for tumor cells which express the MHC I and MHC II genes.

Ostrand-Rosenburg et al disclose a murine sarcoma cell transfected to express syngenic IAk (abstract, lines 14-16). IAk is MHC II in the mouse (abstract, last sentence). MHC II occurs in humans, therefore the limitation of "occurring in humans" in claims 1 and 9 is fulfilled. Ostrand-Rosenburg et al disclose that the SaI tumor is H-2a, KkDd before transfection and confirms the presence of the IAk class II antigen after transfection fulfilling the specific embodiment of claim 9 drawn to tissue typing of the tumor.

Claims 1-3, 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Lindauer et al (Immunology, March 1998, vol. 93, pp. 390-97) or Kerkmann-Tucek et al (International Journal of Cancer, 1998, vol. 77, pp. 114-122).

Claim 3 embodies the method of claim 2 wherein the costimulatory molecules comprise either B7 or CD44. Claim 10 embodies the method of claim 9 wherein the tumor cells are further transfected with one or several genes coding for co-stimulatory molecules and/or cytokines and selected for the expression of these genes.

Lindauer et al disclose the human colorectal tumor cell, SW480 (page 391, first column, under the heading "Cells"), transfected with HLA-DR (MHC II) and B7 (CD80/CD86) (page 393, second column, lines 9-17, under the heading "Class II MHC expression in combination with CD54 and CD80 directly induces T-cell proliferation") thus fulfilling the limitation of claims 2, 3 and 10 drawn to the expression of co-stimulatory molecules and specifically B7. the transfected tumor cells also expressed MHC I (page 393 second column to page 394, first column, bridging sentence). Lindauer et al determined that the SW480 cells lack surface class II expression before the transfection (page 393, second column, lines 1-2 under the heading "Class II MHC expression in combination with CD54 and CD80 directly induces T-cell proliferation"), thus fulfilling the specific embodiment of claim 9 drawn to tissue typing.

Kerkmann-Tucek et al disclose a murine RENCA tumor cell transfected to express both MHC class II and B7(figure 5, "double-transfected"). MHC class II occurs in humans, thus the specific embodiment of "occurring in humans" of claims 1 and 9 are fulfilled.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Dessureault et al (Journal of Surgical Research, 1996, Vol. 64, pp. 42-48).

Dessureault et al teach human melanoma cells transfected with the B7.1 co-stimulatory molecule. Dessureault et al teach that said melanoma cells express both MHC I and MHC II (abstract, lines 3-7 and lines 11-15).

Claims 1-5, 9 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Ostrand-Rosenburg et al (U.S. 5,858,776, filed November 3, 1993

Ostrand-Rosenberg et al disclose tumor cells transfected with B7, MHC class I, MHC class II and cytokines (claims 1, 5, 6, 7, 8 and 17). Ostrand-Rosenberg et al disclose that the tumor cells are from a human patient (column 13, lines 61-64) and that interferon-gamma is a preferred cytokine (column 12, lines 29-35).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindauer et al (Immunology, 1998, vol. 93, pp. 390-97) in view of Abdel-Wahab et al (Cancer, Aug 1997, Vol. 80, pp. 401-412).

The specific embodiments of claims 1-3 and 9-10 and the teachings of Lindauer et al which anticipated these claims are set forth above. Claim 4 is drawn to the tumor cell of any of claims 1-3 wherein one or several genes are also expressed for cytokines. Claim 5 embodies the tumor cells of claim 4 wherein the cytokines are interleukin, GM-CSF, TNF-alpha and interferon-gamma. Claim 10 embodies the method of claim 9 wherein the tumor cells are further transfected with co-stimulatory molecules and cytokines.

Lindauer et al teach tumor cells expressing, MHC I and MHC II and B7, wherein said tumor cells are made by transfections of the genes encoding MHC II and B7. Lindauer et al teach that in a population of cells transfected with DR3, there is a subpopulations that shows partial loss of DR3 expression (page 393, second column, lines 15-17 under the heading "Class II MHC expression in combination with CD54 and CD80 directly induces T-cell proliferation"). Lindauer et al do not teach the transfection of said tumor cells with genes encoding cytokines.

Abdel-Wahab et al teach that immunization of mice with mouse tumor cells transduced to express cytokines induced a strong immune response against a mouse tumor (page 402, first column, lines 11-18). Abdel-Wahab et al teach that tumor cells transduced with genes encoding Il-4, Il-2, interferon-gamma, Il-6, Il-7, tumor necrosis factor-alpha and GM-CSF cytokines have been used for animal vaccinations (page 402, first column, lines 11-18). Abdel-Wahab et al teach that interferon-gamma induces strong anti-tumor immunity by means of direct and indirect mechanisms which include the enhancement of MHC class I and II expression (page 402, first column, lines 18-20 and lines 23-26). Abdel-Wahab et al teach melanoma cells obtained from human patient which are transduced to express interferon-gamma (page 402, second column, under the heading "Preparation of the IFN-gamma Gene-Modified Melanoma Tumor Cells").

It would have been prima facie obvious at the time the invention was made to transfect the tumor cells of Lindauer et al to express interferon-gamma in addition to MHC II and B7. One of skill in the art would be motivated to do so from the teachings of Abdel-Wahab et al on the upregulation of MHC I and II expression by tumor cells expressing interferon-gamma, and the teachings of Lindauer et al on the decrease or loss of MHC II expression in a subpopulation of cells transfected with the MHC II gene. One of skill in the art would be motivated to have MHC II expression in all the cells transfected with the MHC II gene in order to better prime the immune system against the tumor cell.

Claims -3, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dessureault et al (Journal of Surgical Research, 1996, Vol. 64, pp. 42-48) in view of Ostrand-Rosenburg et al (Journal of Immunogenics, 1989, Vol. 16, pp. 343-349).

Dessurealut et al teaches the specific embodiments which anticipate claims 1-3. Dessurealut et al do not teach a method of making a tumor cell comprising the transfection of said tumor cell with MHC II. Dessurealt teaches melanoma cells express both MHC I and MHC II which are transfected with B7. Dessuaralet et al teach that said melanoma cells demonstrated a substantial increase in T-cell proliferation in contrast to melanoma cells transfected with B7 that did not express either MHC I or MHC II, or lung adenocarcinoma cells transfected with B7 which expressed MHC I but not MHC II which did not increase T-cell proliferation (lines 11-16). Dessurealut et al conclude that the expression of all of B7, MHC I and MHC II elicits an improved alloantigenic induced T-cell proliferative response presumably because the presence of both MHC I and MHC II on the cell surface has the capacity to deliver an adequate antigenic-specific signal which is co-stimulated by the B7-CD28 interaction (last sentence of abstract).

Ostrand-Rosenburg et al teach the transfection of a mouse tumor cell with IAk resulting in the expression of both MHC class I and MHC class II. Ostrand-Rosenburg et al teach that the administration of the transfected tumor cells results in the rejection of said tumor cells in mice (abstract, lines 14-22).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to transfect the allogenic MHC I and MHC II genes into melanoma cells which were MHC class I negative and MHC class II negative in addition to the B7 gene; it would also have

been obvious to transfect the lung adenoma cells which were MHC I positive, but MHC class II negative with a gene encoding MHC class II in addition to the B7 gene. One of skill in the art would be motivated to do so through the teachings of Dessurealut et al on the necessity of both MHC class I and MHC class II on the surface of tumor cells in order to generate an adequate antigen-specific signal which is co-stimulated with B7, and the teachings of Ostrand-Rosenburg et al on the demonstration that the transfection of MHC class II into murine tumor cells results in the rejection of said tumor cells in mice.

Claims 1-5, 9 and 10 rejected under 35 U.S.C. 103(a) as being unpatentable over Dessureault et al (Journal of Surgical Research, 1996, Vol. 64, pp. 42-48) and Ostrand-Rosenburg et al (Journal of Immunogenics, 1989, Vol. 16, pp. 343-349) as applied to claims 1-3, 9 and 10 above in further view of Abdel-Wahab et al (Cancer, Aug 1997, vol. 80, pp. 401-412).

The combination of Dessureault et al and Ostrand-Rosenburg et al renders obvious the limitations of claims 1-3, 9 and 10 for the reason set forth above. Neither reference teaches the transfection of the tumor cells with genes expressing cytokines.

Abdel-Wahab et al teach that immunization of mice with mouse tumor cells transsduced to express cytokines induced a strong immune response against a mouse tumor (page 402, first column, lines 11-18). Abdel-Wahab et al teach that tumor cells transduced with genes encoding Il-4, Il-2, interferon-gamma, Il-6, Il-7, tumor necrosis factor-alpha and GM-CSF cytokines have been used for animal vaccinations (page 402, first column, lines 11-18). Abdel-Wahab et al teach that interferon-gamma induces strong anti-tumor immunity by means of direct and indirect mechanisms which include the enhancement of MHC class I and II expression (page 402, first column, lines 18-20 and lines 23-26). Abdel-Wahab et al teach melanoma cells obtained from human patient which are transduced to express interferon-gamma (page 402, second column, under the heading "Preparation of the IFN-gamma Gene-Modified Melanoma Tumor Cells").

It would have been prima facie obvious at the time the invention was made to transfect the tumor cells of to transfect tumor cells with genes encoding B7, MHC in addition to the genes encoding cytokines, especially interferon-gamma . One of skill in the art would be motivated to do so from the teachings of Abdel-Wahab et al on the upregulation of MHC I and II expression by tumor cells expressing interferon-gamma and the teachings of and the teachings of

Dessuraelut et al on the improved alloantigenic induced T-cell proliferative response due to the presence of both MHC I and MHC II on the cell surface of a tumor cell which has the capacity to deliver an adequate antigenic-specific signal which is co-stimulated by the B7-CD28 interaction (last sentence of abstract). One of skill in the art would be motivated to have maintain the MHC I and MHC II expression in all the cells transfected with the MHC genes in order to deliver the antigen-specific signal and thus prime the immune response against the tumor cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at 703-308-4357.

Karen A. Canella

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Primary Examiner, Group 1642
02/08/04